Neoplasms of the Kidney and Adrenal Gland

CLAIR E. COX, M.D., Winston-Salem, North Carolina, and
DONALD R. SMITH, M.D., San Francisco

ALMOST ALL clinically demonstrable neoplasms of the kidney are malignant or have malignant potentialities. Their clinical manifestations often present obscure diagnostic problems. Early suspicion leading to thorough but usually simple diagnostic procedures provides the patient with the best possible hope for survival.

For practical purposes this discussion will be limited to the three most common types of renal tumors. These three, renal cell carcinoma, nephroblastoma (or Wilms' tumor) and carcinoma of the renal pelvis, account for approximately 97 per cent of all malignant renal neoplasms. The remaining 3 per cent are various sarcomatous lesions.

Pathology

Renal cell carcinoma. This tumor accounts for about 75 to 85 per cent of all renal neoplasms. Various names are still applied to this tumor such as Grawitz tumor, hypernephroma, clear cell carcinoma, adenocarcinoma and alveolar carcinoma. The tumor arises in the renal epithelial cells and is generally considered to originate from mature renal parenchyma. There is considerable speculation that renal cell carcinomas may arise from benign renal adenomas. The tumor almost exclusively occurs in adults, usually those in the sixth and seventh decades. Only 51 cases have been reported in children. Males predominate about 2 to 1 and this suggests a hormonal relationship.

The tumor occurs in the left and right kidney with equal frequency and usually arises in one of the renal poles. As the neoplasm expands it compresses adjacent renal tissue and displaces calyces, blood vessels and the pelvis, which then become distorted and tend to surround the mass. With additional enlargement, adjacent organs may be displaced. Metastasis often occurs early in the disease but the lesions are not necessarily related to the size and local extent of the tumor. On many occasions distant metastasis may be the initial symptom of the disease. The tu-

mor may extend directly into the perirenal tissues or by a rich lymphatic network to the regional and para-aortic lymph nodes. Renal vein invasion is common, providing early access to the blood stream. Metastases to the lung are common and often occur early in the disease. The liver and bones are frequent sites of metastatic spread. The vertebrae, pelvis, femur and humerus are the principal osseous sites. Almost every organ in the body has been reported as having been a metastatic site of this disease.

On gross section the tumor usually has a well-defined fibrous capsule. It is yellow and often contains red or brown areas of hemorrhage and necrosis. Cystic degeneration may occur and calcification may be present. Microscopically, varying patterns of cells may be seen even in the same tumor. In general the cells resemble renal tubular cells and have small eccentric nuclei and an abundant clear cytoplasm. At times the cytoplasm may be more opaque and granular, thus leading to the term granular or dark cell carcinoma which some investigators believe is associated with a slightly better prognosis. However, in our experience the type of cell has been of little or no value in determining the prognosis.

Nephroblastoma (Wilms' tumor, embryoma, adenomyosarcoma). This lesion also arises from the renal parenchyma. However, unlike renal carcinoma, the tumor takes its origin from immature renal tissue. It is considered by most investigators to be congenital and to arise from embryonal cells trapped in the kidney. The tumor accounts for about 6 per cent of all renal neoplasms and about 20 per cent of all malignant lesions of childhood. Along with neuroblastoma it is the most common intra-abdominal neoplasm in children. Although Wilms' tumor does occur in adults, it is predominantly a disease of childhood (90 per cent of cases during the first seven years of life) and it has even been reported in the newborn and in fetuses. There appears to be no difference in incidence between the sexes and the tumor occurs with equal frequency in either kidney. It is bilateral in 2 to 5 per cent of the cases. The neoplasm has been found in association with other types of renal anomalies.

Nephroblastoma may arise in any portion of the kidney. It usually becomes large before it is discovered. As with renal cell carcinoma, metastasis often occurs early in the disease, most commonly to the lung. The tumor is covered by a fibrous capsule which is usually intact, but venous and lymphatic invasions are common. Direct extension eventually results in compression of adjacent renal tissue and local metastasis. Renal vein invasion is a common finding at the time of exploration.

The tumors are usually large — often much larger than the kidney. They are often spherical and the surface is smooth or slightly lobulated and is usually covered by large, thin-walled veins. On section the tumor is yellow or grey and heterogeneous; hemorrhagic and cystic areas are often present. Microscopically the major tissues are of connective tissue origin: muscle, cartilage and myxomatous or lipomatous tissue. The epithelial tissue may be undifferentiated or resemble renal tubules or even glomeruli.

Carcinoma of the renal pelvis. About 5 to 10 per cent of all renal neoplasms are carcinomas of the pelvis. The tumors arise from the pelvic and calyceal mucosa and are therefore transitional in cell structure. Rarely, squamous cell carcinoma occurs and it is usually associated with chronic infection or calculous disease. The transitional cell lesions are usually papillary and less commonly are solid or sessile. Their behavior resembles that of the papillary and solid growths of the bladder, which they look like.

The cause of these lesions is unknown, but their tendency to "seed" in the ureter and bladder suggests that the mucosa generally is susceptible to such change. The metabolites of tryptophan have recently been suspected as carcinogenic agents. The uncommon squamous cell lesions seem to be the result of chronic irritation, as from infection or calculous disease.

Some of these papillomata appear benign histologically, but the final opinion must rest with the clinical behavior. The papillary lesions tend to be of lowgrade malignancy and usually do not infiltrate the underlying supporting stroma, yet their clinical course is sometimes most malignant. The solid lesions are usually more anaplastic and are usually infiltrative. Epidermoid varieties are almost always invasive and fatal.

Transitional cell carcinoma of the renal pelvis tends to be multicentric, and similar tumors are often seen in the ipsilateral ureter and bladder. In the bladder the tumors often are close to the ureteral orifice in question. Distant metastasis does occur but is less common than with the renal parenchymal tumors. The regional lymph nodes and the renal vein, however, may be involved. Grossly the papillary lesions are pinkish with many delicate fronds. When they originate near a calyx or the uretero-

pelvic junction, obstruction (hydrocalyx, hydronephrosis or complete obstruction of a renal segment) is produced. Microscopically, these tumors show a central core of connective tissue which is covered by transitional epithelium. Invasion of the supporting structures and underlying muscle is variable.

Symptoms, Signs and Diagnosis

Renal cell carcinoma. Gross total hematuria, usually without pain, is the single most common symptom of renal carcinoma; it occurs in 50 to 80 per cent of cases. The classical triad of pain, tumor and hematuria is uncommon as a presenting symptom complex and its occurrence suggests an advanced neoplasm. Pain simulating renal colic may occur with the passage of clots or tumor tissue down the ureter. The incidence of pain of a more vague nature is variable and is usually a late symptom. Pain or discomfort related to the mass of the tumor is usually of a dull type felt in the back, resulting from ureteral compression, perirenal extension, hemorrhage into the tumor or nerve root irritation. A palpable abdominal mass is also uncommon but occasionally a patient may be first seen because he himself has palpated a renal mass. Patients with certain hereditary diseases such as tuberous sclerosis and Lindau-von Hippel's disease have been noted to have a higher incidence of renal neoplasia.

"Non-urologic" symptoms are exceedingly common and often are the only manifestation of renal carcinoma. In some series one-third of the patients had no clinical indication of renal disease, but instead had vague, seemingly unrelated episodes of nonspecific symptomatology. These nonspecific symptoms, although legion in number and variable in occurrence, may precede the more common symptoms of renal neoplasm by weeks or months. Unexplained fever with or without weakness, anorexia and loss of weight may be present and indeed may sometimes be the only complaint. Gastrointestinal complaints resembling the syndromes of peptic ulcer or gallbladder disease may be the result of renal neoplasia. They are caused by reflex action or by invasion or displacement of contiguous organs. In addition, not infrequently a renal tumor is first brought to notice by the presence of a distant metastatic lesion such as a painful swollen femur or a thoracic tumor observed on routine x-ray examination.

Physical signs are of limited diagnostic value in this disease. The tumor may be palpable but usually it is not. Nonspecific signs of neoplasia often indicate a late stage of the disease. An acute varicocele (usually on the left side) indicates obstruction of the spermatic vein by tumor. In our experience this is exceedingly rare. Other vascular phenomena, a result of vena caval obstruction such as edema of the

legs and dilated abdominal veins, indicate inoperability.

Urinalysis may reveal microscopic hematuria although gross bleeding is more common. Anemia often is present when the disease is advanced. Total renal function is usually not impaired. Polycythemia (erythrocytosis) has recently been noted to occur in 3 to 4 per cent of patients with renal cell carcinoma. This finding is, however, not specific for renal cancer, as evidenced by the recent reports of polycythemia associated with other lesions. Hypercalcemia with or without metastasis to bone has also been noted to occur with renal carcinoma.

The ultimate diagnosis of renal carcinoma depends upon simple x-ray techniques. A plain film of the abdomen often shows enlargement of a kidney and a bulge of its contour. The psoas outline may be obscured if a solid tumor overlies it. If the tumor is a cyst, the psoas may be visible through it. The renal axis may be displaced in any direction, depending upon the location of the tumor. Calcification may be seen within a tumor shadow or in the rim of a "cystic" lesion. A low position of the left kidney cannot be ignored. Excretory urograms usually show a filling defect caused by a space-occupying lesion. The collecting structures, usually the calyces and less commonly the pelvis and ureter, are distorted. Hydronephrosis is rare. Renal function as evidenced by visualization of the collecting structures is usually good and nonfunction strongly suggests renal vein occlusion by the tumor. The diagnostic accuracy of the intravenous urogram is excellent and therefore retrograde pyelograms are not often necessary. They are indicated only in instances in which the function of the contralateral kidney is in question or when intravenous visualization is poor. If the patient has gross hematuria when seen, immediate cystoscopy will demonstrate its source. Postponement of this valuable diagnostic aid is an error, as bleeding from renal tumors is usually intermittent.

Special studies are seldom necessary in the diagnosis of renal carcinoma, as the excretory urogram (or retrograde pyelogram) most often reveals a space-occupying lesion, and if this is coupled with sufficient clinical evidence, usually hematuria, the diagnosis is satisfactorily established. There are, however, definite indications for the various special radiographic and isotopic studies. This occurs when bilateral lesions are suspected, where a space-occupying lesion is found on a "routine" excretory urogram (usually in a patient without urological symptoms) or the age and general condition of a patient would negate surgical treatment if a *reasonable assurance* that a space-occupying lesion was not cancer (a cyst, for example) could be ascertained. Angionephrotomography has its greatest usefulness in the differentiation of renal cyst and tumor. Briefly, this technique involves the rapid intravenous infusion of a bolus of radiopaque material which opacifies vascularized tissues in the kidney. The space occupied by a cyst fails to opacify; a malignant tumor shows increased opacification because of its increased blood supply.

Further differentiation between cyst and tumor can be made by renal arteriography either by the retrograde femoral technique or by direct lumbar needle puncture of the aorta. This procedure demonstrates the renal circulation, produces a dense renal shadow and may show a bulge on renal outline indicating a mass. A cyst will show no positive shadow at all. Due to the great vascularity of a tumor, pooling of the opaque material may occur within it on the delayed films. These two types of studies are therefore of aid in the differential diagnosis of renal space-occupying lesions. However, a positive diagnosis of a cystic lesion can only be made by operative exploration, for it is surprising how commonly cyst and renal tumor are confused, even with proper arteriography and angionephrotomography. Furthermore, 5 to 10 per cent of cysts have cancer in their walls, so all simple cysts must be assumed to be malignant until proved otherwise. In our experience larger cysts and those which contain calcium in their walls are more apt to contain a neoplasm.

If the lesion is intrarenal and at operation the exterior of the kidney appears normal, nephrectomy is the treatment of choice, the clinical history having been considered carefully. Nephrotomy and frozen section biopsy has been suggested, but in our opinion it is contraindicated. Fortunately, most cysts bulge from the exterior of the kidney and the wall may be unroofed, affording inspection of the interior. The presence of hemorrhagic fluid within the cyst is an ominous sign and often denotes malignant change.

Renal scintillation scanning (photoscanning) is a new technique which may prove to be a valuable adjunct in the diagnosis of renal space-occupying lesions. Neohydrin labeled with radioactive mercury is given intravenously and 45 minutes later the renal areas are scanned for radioactivity. The radioisotope concentration of normally functioning renal parenchyma is good and uniform, whereas the concentration over space-occupying lesions is nil, thereby outlining the renal mass. The same results are obtained with cyst or tumor. The photoscan appears to be of considerable help when pyelographic evidence is equivocal and if bilateral lesions are suspected.

Nephroblastoma. The most common symptom and sign of nephroblastoma is a large abdominal mass discovered by the child's parents. Rarely, pain may be experienced by local extension or ureteral com-

pression. Hematuria is unusual but other rather vague symptoms such as anorexia, loss of weight or vomiting are often present. A palpable mass in the flank of a child under six or seven years of age must be regarded as a nephroblastoma (or neuroblastoma of the adrenal) until proved not to be. The liver and lungs may contain metastatic lesions when the child is first seen by a physician.

Renal function and results of urinalysis are usually within normal limits. Urinary cytology is of little or no diagnostic aid. A plain abdominal x-ray film will reveal a mass in the kidney region, often with displacement of bowel and indication of stomach gas. Intravenous urograms most often establish the diagnosis by revealing pronounced distortion of the pelvis and calyces, although sometimes the dye is not excreted. Retrograde pyelograms, if necessary, will reveal in more detail the intrarenal distortion caused by a space-consuming lesion. A suprarenal lesion (neuroblastoma) may cause displacement of the kidney but without distortion of the intrarenal structures. Special radiographic and isotopic studies cannot significantly improve on the diagnostic accuracy of the urographic or pyelographic examinations.

Carcinoma of the renal pelvis. The signs and symptoms of this tumor are not unlike those associated with the much more common parenchymal carcinoma of the kidney. The most common symptom is massive hematuria, usually without pain but occasionally associated with colic due to clot or tumor bolus passage or with dull flank ache due to hydronephrosis or hydrocalyx. Urograms in the case of patients with bladder carcinoma (which we do routinely) may occasionally reveal a renal pelvic carcinoma. It is not uncommon for this lesion to be discovered some years after the diagnosis of bladder carcinoma.

Physical examination is usually not helpful. Tenderness may be present if hydronephrosis exists and generalized signs of carcinoma may be obvious. The urine may contain blood cells but this symptom is often intermittent. Infection may be present and in our experience the coccal organisms are often the infecting agents. The methylene blue stain of the urinary sediment (which is done on all urologic patients) may reveal epithelial cells. Squamous epithelial cells are normal in the urine of females and in males taking estrogens for the control of cancer. However, transitional epithelial cells are distinctly abnormal unless there is a urinary tract infection. Therefore, the presence of transitional epithelial cells, especially if abnormal in appearance (large nuclei and in clumps) strongly suggests a transitional carcinoma of the urinary tract. Further x-ray studies are of course required to pinpoint the site of the lesion.

Intravenous urograms or, if necessary, retrograde pyelography will establish the diagnosis in almost all cases. Unlike renal cell carcinoma, where a filling defect in the renal parenchyma is noted, these lesions basically produce filling defects in the pyelocalyceal system with or without varying degrees of hydronephrosis or hydrocalyx. The lesion may arise near the ureteropelvic junction and produce hydronephrosis or even nonfunction. The basic pattern of a filling defect often leaves one with a differential diagnosis of tumor, nonopaque stone or blood clot. Operative exploration is often necessary, especially if the clinical course is not helpful. Tuberculosis may mimic renal pelvic carcinoma, and urinary acid-fast studies are therefore sometimes indicated. Special radiographic studies are rarely needed.

Treatment and Prognosis

Renal cell carcinoma. Nephrectomy including *en bloc* removal of the perinephric fat is the treatment of choice. The ureter need not be removed. The nephrectomy may be accomplished transabdominally, transthoracically or through the conventional flank approach, depending upon the anticipated technical details, the experience of the surgeon and the physical stature of the patient. To prevent intravenous infusion of tumor cells, the renal vein or entire renal pedicle should be ligated before the kidney is manipulated.

Occasionally renal lesions may not be discernible either visually or by palpation at the time of operation. It is our opinion that if a preoperative diagnosis of a space-consuming lesion has been properly made and the other kidney is normal, nephrectomy is indicated regardless of normal appearance. If a simple "blue-domed" cyst is encountered, the wall should be excised. Papillary growths within the cyst require that nephrectomy be performed. Hemorrhagic cysts should be treated as neoplasms requiring nephrectomy.

Nephrectomy is generally contraindicated if metastatic lesions are demonstrable. Regression of such lesions after removal of the renal primary has been reported, but this is exceedingly rare. In addition, nephrectomy may be contraindicated if the tumor is considered to be large and fixed or if the general condition of the patient is too poor to permit operation. Renal vein invasion, which can be anticipated by the absence of function by intravenous urograms, also may preclude operative treatment. In rare instances severe hemorrhage may necessitate nephrectomy even in the presence of metastasis. Erythrocytosis, hypercalcemia, fever and other generalized symptoms usually disappear after nephrectomy but may recur if metastasis occurs.

Renal cell carcinoma and lesions metastatic from it are usually quite radioresistant. Most authorities

agree that x-ray therapy is therefore not indicated either preoperatively or postoperatively but that it may be used palliatively to control the primary tumor, or osseous metastasis. There are a few proponents of x-ray therapy in this disease but the results they report are difficult to evaluate. Chemotherapy also has been generally unsuccessful in the management of renal adenocarcinoma. However, the possibilities in this field continue to be explored and one can only hope that the newer chemotherapeutic agents will be less toxic and more effective.

The prognosis in this disease is poor. About 25 per cent of the patients are alive five years after nephrectomy. The outlook is worse if the renal vein is involved, if distant metastasis has occurred, if the histologic grade is high and if the tumor is large. Not uncommonly metastatic lesions develop ten to fifteen years after removal of the primary growth. The percentage of cure can only be increased by more intensive urologic investigation of patients with hematuria, microscopic or gross, persistent, transient or intermittent.

Nephroblastoma. For nephroblastoma, nephrectomy combined with radiation therapy is the treatment of choice. In 1959 Klapproth reviewed the world literature and reported 282 cases treated by nephrectomy alone. This group had a 20.9 per cent cure rate. A cure rate of approximately 30 per cent can be attained by the combination of radiation therapy and nephrectomy. There is no unanimity of opinion as to whether the x-ray therapy should be given preoperatively, postoperatively or both; and there is no good statistical evidence to support any one method. In general, for various technical reasons, most surgeons prefer nephrectomy followed by radiation therapy. Preoperative radiation therapy usually decreases the vascularity and causes dramatic shrinkage of the tumor in one or two weeks. (If this does not occur, the diagnosis of Wilms' tumor should be reconsidered.) This is helpful if a large tumor is to be removed through the flank but we prefer the transperitoneal approach for renal tumors in children, and therefore tumor size is less important.

If metastasis has occurred, nephrectomy is usually not indicated. However, x-ray therapy will usually cause rapid regression in the size of the primary and also the metastatic sites. These tumors and the metastatic lesions are very radiosensitive. In addition, chemotherapy has recently been demonstrated to have a palliative effect on them. The most useful chemotherapeutic drug is actinomycin D.

In the absence of demonstrable metastasis, about 30 per cent of patients will be cured by radiation therapy and nephrectomy. About 85 per cent of the children who do not survive this disease die within

the first year. Some observers feel a cure may be assumed if the child survives for two or three years, but Riches has stated that metastasis has been reported five years after nephrectomy and local recurrence after eight years. In general, the younger the child at the time of diagnosis and treatment, the better the prognosis.

Renal pelvic carcinoma. The treatment of choice is nephroureterectomy with excision of the periureteral portion of the bladder. This radical approach is contraindicated if metastasis has occurred. However, even if distant metastatic disease is present, nephrectomy may be indicated for relief of pain or bleeding. Unlike their histologic counterpart occurring in the bladder, renal pelvic tumors are radioresistant. Irradiation therapy is therefore of little benefit.

The prognosis is better than for renal parenchymal carcinoma. This is especially true for the more benign, non-infiltrating papillary lesions, but less so for the solid infiltrating lesions and the squamous cell variety. Fifty to 75 per cent of patients with lowgrade malignant disease are alive after five years. Those with more undifferentiated solid lesions have a five-year survival of about 25 per cent or less. Epidermoid carcinoma is almost always fatal within one year.

Sarcomas comprise about three per cent of all renal malignant neoplasms. They are made up of smooth or striated muscle, fibroblastic tissue or fat and may become quite large, filling the flank. The signs and symptoms are usually the presence of a mass and local pain. Hematuria is not common. Spontaneous perirenal hemorrhage may cause the first symptoms. The diagnosis is essentially the same as for renal cell carcinoma. Preoperative differentiation from other mass lesions is impossible. Treatment is nephrectomy and the prognosis is poor.

The kidney is a common metastatic site for tumors. In one large series of 649 autopsies performed on patients with carcinoma, metastasis to the kidney was found in 42, 32 of which were from the bronchus. Most of these metastatic lesions are unapparent clinically. If hematuria does occur, it is difficult to differentiate metastatic disease from primary renal carcinoma.

As was stated previously, benign renal neoplasms are usually asymptomatic and are not seen by pyelography. Occasionally these renal adenomata may become big enough to simulate a renal carcinoma and they should then be treated as such, because the preoperative diagnosis of benign renal adenoma is impossible.

ADRENAL GLAND

Neoplasms of the adrenal gland in almost all cases present clinical symptoms and signs which are pecu-

liar to the type of adrenal hormones that they are elaborating in excess. Therefore, clinically important and recognizable adrenal tumors are described as being endocrine tumors. These lesions may arise in the cortex or the medulla of the adrenal. Non-endocrine adrenal tumors are clinically rare and are usually benign.

Tumors of the adrenal cortex are principally the cortical adenoma and cortical carcinoma. (Cortical nodules are a frequent autopsy finding and may be the source of the adenomas and carcinomas.) Non-functioning adrenal cortical tumors, both malignant and benign, have been reported but are unusual. It is often difficult to distinguish between cortical carcinoma and adenoma histologically and the differentiation often depends on clinical behavior, endocrine studies and evidence of metastasis. Tumors of the adrenal medulla are derived from primitive nerve tissue common to the sympathetic ganglia and the medullary tissue. Pheochromocytoma is the common tumor of this type. This lesion is rarely malignant in that metastasis is most unusual and local invasiveness is not common. The highly malignant neuroblastoma of the adrenal medulla which is seen in infancy and childhood was discussed under the differential diagnosis of Wilms' tumor of the kidney. This lesion ordinarily presents as an abdominal mass in a young child. Most of these tumors excrete dopamine and norepinephrine which are converted into homovanillic and vanilmendalic acids. Excessive amounts of one or both of the latter substances are therefore usually found in the urine. The treatment is operation and roentgen therapy.

The clinical diagnosis of an adrenal tumor in almost all cases is suspected by the presence of signs and symptoms produced by the overproduction of adrenal hormones. Diagnostic studies proceed along two basic lines: (1) anatomic or radiologic methods to show the actual presence of an adrenal mass, and (2) endocrinologic investigations which measure the type of and the amount of hormones which are being excessively produced, thereby identifying the tumor type.

Radiologic investigation should begin with an excretory urogram. A soft tissue shadow may be noted above the kidney and the kidney may be displaced by a suprarenal mass. The calyceal system is ordinarily not distorted, as adrenal tumors rarely invade the kidney. Because they are small, many adrenal tumors (and hyperplasia) are not seen by this screening test. Presacral pneumography (retroperitoneal gas study) has proved to be of great value in outlining the adrenal glands and is the single best anatomic method of demonstrating an adrenal tumor. A few of the smaller tumors (and hyperplasia) may not be seen by this study but because it is simple to perform and has been innocuous in our

hands, it is indicated whenever an adrenal tumor is suspected. Aortography of adrenal tumors has been unrewarding but some success has recently been reported with pheochromocytomas.

Tumors of the adrenal cortex produce three basic endocrinologic syndromes, depending upon the type of hormones which are being elaborated in excess: (1) adrenogenital syndrome and its variants: virilization, precocious puberty and feminization; (2) Cushing's syndrome; and (3) primary aldosteronism. These diagnoses can be established by clinical evaluation of the patient, radiographic studies and endocrinologic data.

The "adrenogenital syndrome" and its variants are produced by disorders (tumor or hyperplasia) in the zona reticularis of the adrenal cortex. The classic example is the congenital adrenal syndrome seen primarily in newborn female infants and caused by adrenal hyperplasia due to an enzyme block in the production of hydrocortisone, with a resultant overproduction of adrenal androgenic substances. Virilization (intersexuality) is the predominant feature, along with variable metabolic and electrolytic defects. If this syndrome occurs after birth or up to the age of 12 (acquired adrenogenital syndrome), it is usually, if not always, due to tumor. Again the basic feature is virilization (but without intersexuality) in the female and, less commonly, precocious puberty in the male. (Precocious puberty in young males is rarely due to adrenal tumor). In addition to virilization the overproduction of androgens in these children produces rapid growth, increased muscularity and premature closure of the epiphyses. Frequently signs and symptoms of Cushing's syndrome (hydrocortisone overproduction) are present in addition to the virilizing androgenic effects. The adrenogenital syndrome (usually some degree of virilization) may occur in the adult female, and in about 50 per cent of the cases this is due to tumor. The diagnosis of virilizing adrenal disorders is made by the finding of an overproduction of androgenic metabolites (17-ketosteroids) in the urine. If the condition is due to tumor, the 17-ketosteroid levels are often very high and are not influenced by tests of suppression and stimulation. Feminizing adrenal cortical tumors which usually produce gynecomastia in the male child and adult are uncommon.

Cushing's syndrome is produced by hyperplasia or tumor of the zona fasciculata of the adrenal cortex. The metabolic abnormality is an overproduction of hydrocortisone which is measured in the urine as 17-hydroxysteroids. The classic full-blown stigmata of Cushing's syndrome are familiar to every medical student and need not be repeated here. The clinical diagnosis is less clear when the syndrome is mixed with signs of excess androgen production (virili-

zation) or where the problem is one of obesity plus hypertension, menstrual irregularities or hirsutism. Tests of stimulation and suppression are helpful in the diagnosis, particularly in the preoperative differentiation of tumor and hyperplasia. In children up to the age of ten the disease is almost always due to tumor. In adults most cases are in women and many are due to hyperplasia. The treatment of Cushing's syndrome caused by tumor is surgical removal.

Primary aldosteronism is a syndrome produced by the excess secretion of aldosterone by the zona glomerulosa of the adrenal cortex. The syndrome is usually caused by a single functioning tumor which is most often benign. In a few instances multiple adenomas and hyperplasia have been found. The usual features of this syndrome are hypertension, which may be mild, low serum potassium with symptoms of potassium depletion such as muscle weakness and fatigue, and an excess excretion of aldosterone in the urine. Hypocalcemia is common but may be absent at certain times and a metabolic alkalosis may be persistent. Many of the patients do not have the classical features of the disease and the diagnosis can therefore be difficult. A useful diagnostic test is the administration of an aldosterone antagonist such as spironolactone which will block the renal tubular effects of aldosterone. In addition, patients with this syndrome have an increased total plasma volume, and this is not found in essential hypertension and Cushing's syndrome. As the tumors are generally small (1 to 3 grams) radiographic demonstration is often impossible. The treatment is surgical excision of the tumor; and if preoperative localization is not obtained, bilateral exploration is necessary.

Functioning tumors of the adrenal medulla (pheochromocytomas) are among the most interesting tumors in medicine. They secrete excess amounts of norepinephrine and epinephrine which are measured in the urine as catecholamines. These tumors occur with equal frequency in males and females, most commonly between the ages of 20 and 50. About 90 per cent are located in one adrenal gland but rarely they are bilateral. Extra-adrenal tumors occur in about 10 per cent of the cases, especially along the para-aortic area and occasionally within the bladder. The characteristic feature of the disease is paroxysmal hypertension but many patients have sustained or malignant hypertension. The paroxysmal attacks of hypertension are associated with varying symptoms of anxiety, headache, sweating, nausea, pallor and precordial distress. The prolonged effect of the excessive release of norepinephrine and epinephrine often leads to sustained hypertension and a hypermetabolic state associated with glycosuria. There are two basic types of tests which provide a presumptive diagnosis of pheochromocytoma: (1) Those designed to stimulate the excretion of norepinephrine and epinephrine from the tumor, such as the histamine test and (2) tests designed to inhibit the pressor substances and thus lower the blood pressure, such as the regitine test. However, the best evidence for the presence of the tumor is the direct measurement of urinary and plasma catecholamines. Unfortunately, these levels may not be significantly elevated between paroxysms of hypertension and the diagnosis may therefore depend on a combination of all available diagnostic aids. Preoperative localization of the tumor by radiographic means is usually possible. Treatment of the tumor is surgical excision. Cautious preoperative and postoperative medical management is essential since patients with this disease often have a low blood volume, necessitating preoperative transfusion.

The most direct surgical approach to all adrenal tumors is through the flank, either extrapleural or transpleural. However, if preoperative localization has not been possible, the transabdominal approach or bilateral flank approach is necessary.